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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/483,837	SHARMA, SHUBH D.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,43-50,52-66 and 68-81* is/are pending in the application.

4a) Of the above claim(s) *60-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,43-50,52-59,63-66 and 68-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JC

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/29/04 has been entered.

Election/Restrictions

In view of applicant's arguments that the previous claims contain a claim to a metal, the restriction, by original presentation is withdrawn.

Status of Claims

Claims 41, 43-50, 52-66, 68-81 are pending in the application.

Claims 60-62 are withdrawn from consideration as being directed to a non-elected invention.

Claims 41, 43-50, 52-59, 63-66 and 68-81 are under consideration.

Withdrawn Objection and Rejection

In view of the amendments to the claims and applicant's arguments, the rejection under 35 USC 102/103 over Francis et al and 103 over Kay is withdrawn. The objection to the oath/declaration is withdrawn in view of the new declaration on file.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 41, 43-50, 52-59, 63-66 and 68-81, as amended, are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specifically asserted utility or a well established utility for reasons set forth in the last Office action (7/27/04).

Response to Arguments

Applicant argues that independent claims 41 and 50 have been amended to more specifically define the structures. The transitional language in the preamble has been changed to "consists of." Additionally, the structures are now defined as a solid phase bound library with each constituent member consisting of between four and about twenty amino acid residues,

with three forming a metal ion-binding backbone for binding to either technetium or rhenium, and to provide that the library members comprise a sequence of no more than "about twenty amino acid residues." It has been made explicit that such sequences, when the metal ion-binding backbone is complexed with a metal ion, form conformationally constrained reverse turn structures, which mimic reverse, turn structures. Applicants further argue that the complexation of a tripeptide sequence including at least one residue with an available sulfur atom for complexation to either a technetium or rhenium metal ion forms a conformationally constrained secondary structure, which is a mimic of a reverse turn structure. Reverse turn structures are well-known in the biological sciences, and many, if not most, receptor-ligand interactions involve a reverse turn structure.

In response, per applicant's argument the sequences are complexed with a metal to form the reverse turn structures. However, there is no sequence in the claims or a reverse turn structures. The claims define the library in terms of words. Compounds, especially a complex one, as a library has to be defined either by its primary structure i.e. peptide sequences. The claimed wordings describe only an "about 20 amino acids" comprised in the library, without indicating the peptide sequence of these 20 amino acids. Neither does it describe the

metal-library complex that results in a conformationally constrained reverse turn. The claims do not show which residues e.g., tripeptide is complexed with a metal that cause a reverse turn mimic. It matters not that the transitional language is now "consists". This is no different from the transitional language "comprise" as the structure of the compound library is not defined or contains numerous variations thereof.

It is argued that there is nothing about "screening" per se that may appropriately be asserted in a 35 U.S.C. 101 rejection. MPEP 2107.01 discusses, there is no proper rejection on the grounds that an invention is a research tool. Because, in part, of the specific and recognized utility of mimics of reverse turn structures, the invention as now claimed has both a specifically asserted utility and a well-established utility. The specifically asserted utility is discussed throughout the application. The application accordingly discloses use of libraries directed toward integrin receptors that recognize the RGD sequence; tuftsin receptors; peptide hormone receptors, such as somaotstatin, cholecystokinin. opioid, melanotropin, LHRH. tachykinin and similar peptide hormone receptors provide specific guidance on how to construct and use libraries. The utility is well established because the importance of reverse

turn structures in receptor binding is well known. Libraries which provide mimics of such structures inherently have utility.

In response, the property a reverse turn mimic exhibited by the library is not a specific utility, albeit it might be considered important for a library function. There is no correlation of the inherent utility provided by a reverse turn structures. The claims do not recite for any peptide structures or sequences hence, its binding to the different receptors is unclear. Binding as stated in the last Office action is a screening for a member lead compound, which is not a specific utility of the library per se.

Claims 41, 43-50, 52-59, 63-66 and 68-81 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specifically asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

See the response above.

Claim Rejections - 35 USC § 112, first paragraph

Claims 41, 43-50, 52-59, 63-66 and 68-81, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific library

that binds to rhenium or technetium metal, does not reasonably provide enablement for any type of combinatorial library with at least three residues that form a metal-ion binding domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record (7/27/04).

Response to Arguments

Applicant argues that both rhenium and technetium metals are used throughout the specification, and that rhenium and technetium are taught as having similar chemistries and being substantially interchangeable. It is additionally argue that a number of actual examples of complexation with technetium is described throughout the specification. Claims 41 and 50 have been amended such that the metal ion-binding domain is specific for technetium or rhenium ions.

In response, the enabling disclosure is not in reference only to the use of metals. This is only one of the numerous broad scope of the claimed library. Rather, as stated in the last Office action, the library as complex to rhenium or technetium metal, i.e., the whole broad complex. It encompasses numerous, undefined components in the library. It does not define the kind of amino acids of the about 20 residues

contained in the library. Neither does it define which of the 20 residues is the tripeptide that forms a complex with Re or Tc metal or the location, kind and/or number of sulfur atom that bind to a metal to form a conformationally constrained reverse turn. The specification at page 19, line 17 up to page 22, line 10 refers to the two RGD receptors and Tuftsin receptor mimics. It is not apparent from the structure, what is considered a mimic or if the structure is a combination of a mimic or a peptide. The specification does not enable any derivative for X when the metal ion valences are not satisfied (claim 71). To therefore determine the different, numerous undefined molecules of the claimed library would require undue experimentation. The broad scope of the claimed invention is not enabled for its full scope.

Claims, 41, 43-50, 52-59, 63-66 and 68-81, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is reiterated below.

Claims 41, 43-50 and 52-59, as amended, which recites "…unique selection or sequence occurs in the one or more amino acid residues… at the N or C-terminus of the metal ion-binding backbone….." is not supported in the as-filed specification. MPEP 714.02 recites that applicants point out where specifically support for the new limitations appear.

Response to Arguments

Applicant asserts that claims 41 and 50 have been amended to more clearly describe the invention. It is asserted that the difference in either "the selection or the sequence" may be in any part of the library member, including either the metal ion-binding domain or residues at either or both the N- or C-terminus. There is clear support in the specification for the "unique sequence being either in the metal ion-binding domain or outside the metal ion-binding domain." See, e.g., page 32, line 19 bridging page 33, line 5, inter alia.

In response, none of the cited sections reveal the alternative claimed "selection or sequence". [It does reveal unique but has been obviated with its cancellation in the present claim.] The alternative language is not only supported in the original disclosure but also is confusing with respect to the use of said alternativeness.

Also, the presently amended claim drawn to a "predetermined' sequence does not have clear support in the original disclosure. There is no description in the original disclosure or definition as to the predetermined sequences of between four and 20 residues. Furthermore, claim 71 recitation of R1 and R2 "together comprise at least one amino acid" and "which mimics a reverse turn structure upon complexation of a metal ion to X" in the context of the claim does not have clear support in the disclosure. (Cf. with Fig. 1). MPEP 714.02 clearly states that applicant points out where in the specification support for the new limitations can be found.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 43-50, 52-59, 63-66 and 68-81, applied to the amended claims, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In view of the amendments to the claims and applicant's arguments, the rejection of the previous claims is withdrawn.

However, the following rejections are applied to the newly amended claims.

1. Claim 41 is unclear as to the predetermined sequence of amino acid residues, especially in the absence of positive support in the specification. The specification does not provide a definition or determination of such predetermined residues. Furthermore, the alternativeness of the claimed "selection or the sequence" is unclear. The claim is drawn to a compound library. Hence, "selection", which is a method step would appear inappropriate as an alternative to a sequence. The recitation of "sequence" would suffice.

2. Claim 72 does not add further limitation to claim 1 which already recites Re and Te metal ion.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 41, 43-49, 63-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24-25, 30 and 31 of copending Application No. 09/883,069. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed combinatorial library described in terms rather than structures is similar, if not nearly the same, as the '069 library defined in terms of its structure. The instant claimed conformationally mimic would be considered an inherent property of the structure of the '069, conformationally constrained by the sulfur of the cys residue. [It is of interest to note applicant's statement above that the reverse turn structures are well-known in the biological sciences, and many, if not most, receptor-ligand interactions involve a reverse turn structure.]

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41, 43-50, 52-66, 68-81, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Hnatowich et al (U.S. 5,980,861).

Hnatowich et al discloses at col. 15, line 15 up to col. 18, line 23 a library comprising of protein-nucleic acid, a chelator (a metal ion-binding domain including a S-protected group as claimed) and radionuclide. libraries of chelators, nucleic acid-chelator compounds, and nucleic acid-chelator-radionuclides are useful for rapidly screening for compounds with desired properties, e.g., low non-specific binding, selected lipophilicity, high or low affinity for radionuclides. At col. 17, line 20, Hnatowich discloses the library of solid bound chelator including a S-protected group. Hnatowich discloses that chelators which bind to radionuclides are known in the art. Chelator moiety will be a tetradentate chelator, i.e., will be capable of four-point binding to a radionuclide. Also, an N2 chelator can chelate a radionuclide through two nitrogen atoms (e.g., amido nitrogens, e.g., of a peptide backbone) and two sulfur atoms (e.g., of a mercaptoacetyl moiety), while N3 chelators can chelate to a radionuclide through three nitrogen atoms and one sulfur atom. The chelator

moieties include amidothiols, including, e.g., mercaptoacetyltripeptides, e.g.,mercaptoacetyltriglycine, mercaptoacetyltriserine. Mercaptoacetyl-tripeptides can chelate radionuclides by coordination through the three amide nitrogens of the peptide backbone, and the terminal mercapto group. (See col. 10, line 66 up to col. 11, line 60). Hnatowich discloses at col. 2, lines 59-67 the radionuclides as selected from the group consisting of rhenium 186, rhenium 188 and rhenium 189. Hnatowich defines at col. 3, lines 14-65 the amino acid as an oligopeptide, e.g., mercaptoacetyl tripeptide, i.e., a tripeptide covalently linked (preferably at the amine terminus) to a mercaptoacetyl moiety, i.e., --C(O)--CH2-SR, wherein R is hydrogen or a protecting group. The mercapto group is protected, preferably as a lower alkyl thioester, e.g.,--S--C(O)-lower alkyl, prior to chelation with the radionuclide. Protecting groups for sulfur are known. The sulfur protecting group can be removed under mild conditions to unveil the free mercapto group, which can then participate in chelation of a radionuclide. The term peptide is defined to include two or more amino acids covalently attached through a peptide bond. Amino acids, which can be used in peptide molecules, include those naturally occurring amino acids found in proteins such as cysteine, arginine, proline, histidine, phenylalanine, tyrosine, and tryptophan. The term "lower alkyl" refers to an alkyl group having from 1 to 6 carbon atoms. Exemplary lower alkyl groups

include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and n-hexyl.

Hnatowich discloses all of the claimed features except that the peptide sequence employed by Hnatowich is PNA i.e., peptide-nucleic acid. However, the claims even with the recitation of the transitional language consist, does not define any structure, as opposed to Hnatowich's definite structure. Hnatowich, like the claimed invention, discloses the binding domain (chelator) as a peptide sequence including a S-protected group. Hnatowich also discloses that said chelator has been done exclusively for peptides. The claimed invention would have been obvious to one having ordinary skill in the art at the time the invention was made. The reverse turn structures would be obvious in view of applicant's statement above that the reverse turn structures are well-known in the biological sciences, and many, if not most, receptor-ligand interactions involve a reverse turn structure. All the features of the claimed are disclosed or at least suggested by Hnatowich.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D.

Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0812. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
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Tdw